UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,925	09/24/2003	William Hildebrand	66802.055	4622

30589 7590 09/16/2010

DUNLAP CODDING, P.C.
PO BOX 16370
OKLAHOMA CITY, OK 73113

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
09/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,925	HILDEBRAND ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/24/10 & 8/16/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42,45,46,48-51,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *38-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-37, 42, 45, 46, 48-51, 60 & 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/16/10 has been entered.

Applicant's amendment and response filed 5/24/10 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I and species of ELISA plate as the substrate, antibody as the anchoring moiety, W6/32 as the antibody, as well as Applicant's election of the species of HLA-A2 with traverse in Applicant's amendment and response filed 12/1/06.

Claims 31-37, 42, 45, 46, 48-51, 60 and 61 are currently being examined.

3. Applicant's amendment filed 5/24/10 has overcome the prior rejection of record of claims 31-37, 45, 46, 49-51, 60 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

4. Applicant is reminded that for the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.*, 9/24/03, as the parent applications do not support the claimed limitations of the instant application. The provisional parent application serial no. 60/413,842 only discloses ELISA assays using W6/32 or pan-HLA antibody immobilized HLA to detect anti-HLA antibodies. The provisional parent application serial no. 60/474,655 discloses some aspects of making soluble HLA from gDNA or cDNA. The parent application serial no. 10/337,161 and 10/022,066 disclose soluble HLA and making soluble HLA, respectively. In addition, the provisional parent applications do not disclose "pool" in the context of the claimed method.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 31-37, 42, 45, 46, 48-51, 60 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method for detecting anti-MHC antibodies in a sample, wherein the anti-MHC antibodies are class I

MHC antibodies and the MHC complexes made and utilized in the claimed method are class I MHC complexes, does not reasonably provide enablement for detecting anti-MHC class II antibodies, wherein the MHC complexes made and utilized are MHC class I or class II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or used the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass making and using a class I MHC complex with host cell derived β2m detecting anti-MHC antibodies that can be other than anti-class I MHC antibodies

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used except for making class I MHC complexes and detecting the presence of anti-class I MHC antibodies in a sample.

The instant claims recite that a MHC heavy chain is transfected into a host mammalian cell line wherein it binds to endogenous β2m from the host cell.

The specification discloses no working examples with regards to making and using class I MHC complexes for other than detecting antibodies that are not MHC class I antibodies, nor guidance for doing so.

Evidentiary reference Fix teaches that MHC class I heavy chain binds β2m, whereas MHC class II is comprised of α and β chains, but not β2m.

Thus, the evidentiary reference teaches that MHC class I is comprised of β2m but MHC class II is not, and thus it flies in the face of scientific reason that the claimed method could be used to detect anti-MHC class II antibodies.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 42 recites the limitation "class II MHC" in line 4. There is insufficient antecedent basis for this limitation in the claim2, as the base claim 31 recites that the β2m in the mammalian host cell line associates with the MHC heavy chain molecule and the

endogenously loaded, naturally produced peptide ligand. Class II MHC does not associate with β2m, but rather associates with a β chain that is not β2m.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 31-37, 42, 45, 46, 49-51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of McClusky *et al* (J. Immunol. 1988 141: 1451-1455), Prilliman *et al* (Immunogenetics, 1997, 45: 379-385, IDS reference), DiBrino *et al* (Biochemistry 1995, 34(32):10130-10138, of record), Hausmann *et al* (Clin. Exp. Immunol. 1993, 91: 183-188) and Chen *et al* (J. Immunol. 1994, 152: 2874-2881).

U.S. Patent No. 5,482, 841 discloses an assay method for detecting the presence of anti-HLA antibodies in a sample, said assay comprising use of HLA molecules extracted from cells and purified by detergent extraction (*i.e.,* full-length MHC class I molecules that comprise the TM and cytoplasmic regions), centrifugation, PEG and NH_4SO_4 precipitation, said HLA molecules indirectly linked to a solid support such as beads, membranes and microtiter plates by polyclonal or monoclonal antibodies specific for the α3 domain of Class I HLA or the associated β2m chain or to a conformational epitope expressed by the combination of both chains, or specific to epitopes conserved across a class or subset of HLA molecules, such as ones specific for HLA-A, B or C. Thus, the art reference inherently discloses that the full-length, detergent-extracted HLA complexes are occupied with endogenous peptides (*i.e.,* because of the isolation protocol, the HLA molecules retain their conformation that is dependent upon peptide being bound in the HLA binding groove, as evidenced by detection with conformation dependent anti-HLA antibodies).

U.S. Patent No. 5,482, 841 further discloses that a sample containing antibodies is added, then bound antibodies are separated from free antibodies and other non-specifically bound proteins or other components, and the presence of the antibodies is detected using a labeled reagent such as anti-human antibody against IgG, IgM or IgA. U.S. Patent No. 5,482, 841 discloses that the samples may be biological fluids such as blood, CSF, tears, saliva, lymph, dialysis fluid, organ or tissue culture derived fluids and fluids extracted from physiological tissues. U.S. Patent No. 5,482, 841 discloses that of particular interest are allo-antibodies found in the serum of transplant or prospective transplant patients, and that the determination of the presence and specificity of antibodies against foreign HLA antigens is therefore clinically important for monitoring transplant patients, and the assay may test for reactivity against a panel of antigens or may be specific for a single donor. U.S. Patent No. 5,482, 841 discloses that the solid

support can be microtiter plates (with wells), glass, plastic, polysaccharides, nylon or nitrocellulose [membranes] or paramagnetic component materials surrounded by plastic. U.S. Patent No. 5,482, 841 discloses using negative and positive control samples. U.S. Patent No. 5,482, 841 discloses a kit for use in a method for detecting at least one receptor analyte specific for an HLA antigen in a biological sample, said kit comprising a solid support coated with a capture agent capable of specifically binding to a conserved region of a subset of interest of HLA antigens and a labeled reagent that specifically binds to human antibodies, and wherein the capture agent may be an antibody directed to the α3 domain of HLA class I heavy chain (see entire reference).

U.S. Patent No. 5,482, 841 does not disclose wherein the HLA molecules in the assay method are those produced by the method steps recited in the instant claims, *i.e.,* wherein the HLA class I molecules are soluble, truncated molecules that consist of the class I MHC heavy chain and endogenous β2m and peptide from the mammalian host cell.

U.S. Patent No. 5,482, 841 does not disclose wherein the MHC class I heavy chains are obtained by isolating mRNA from a source, wherein the mRNA encodes an MHC heavy chain allele, reverse transcribing the mRNA to obtain cDNA and identifying an individual MHC class I heavy chain allele in the cDNA.

McClusky *et al* teach that their complex of soluble class I heavy chain (a soluble murine MHC class I heavy chain consisting of the α1α2 regions of H-2D^d and the α3 and carboxyl-terminus of Q10^b (which is a secreted protein)) plus the non-covalently-associated β2m from the host cell (L cells) is especially valuable because it is a monovalent, soluble, homogenous, recombinant protein, free of detergent, lipid or cellular membrane components. McClusky *et al* teach isolation of the complex using anti-H-2D^d antibodies coupled to Sepharose-4B, subsequent elution from the immunoaffinity column at pH 11.5 and subsequent neutralization. McClusky *et al* teach that the antigen-specific TCR of effector T lymphocytes recognizes antigenic peptide in the context of self MHC class I and that consequently, such complexes are useful for the study of MHC/TCR interactions (especially second full paragraph at column 1 on page 1454, reference 8, materials and methods and introduction sections, and last paragraph of reference).

Thus, McClusky et al teach producing an intact, soluble chimeric murine MHC class I complex occupied with endogenous peptide in the binding groove that is especially valuable because it is a monovalent, soluble, homogenous, recombinant protein, free of detergent, lipid or cellular membrane components, but do not teach truncating a non-chimeric class I MHC heavy chain to exclude the transmembrane and cytoplasmic domains using a PCR primer.

Prilliman *et al* do provide this teaching as follows, as well as method steps recited in the instant claims, exclusive of those involving mRNA. Prilliman *et al* teach large-scale production of Class I HLA in roller bottles (*i.e.,* in a large scale mammalian tissue culture system) for expansion of transfected cells for inoculation into a hollow fiber bioreactor unit for high yield production of soluble class I HLA. Prilliman *et al* teach a full-length, single stranded cDNA clone of HLA-B*1501 used as a template in PCR amplification with primers, the 3' primer introducing a TGA stop codon, truncating the expressed form of the molecule through removal of the transmembrane and cytoplasmic exons from the coding region. Prilliman *et al* teach the pCR product is directionally subcloned into M13, and then subcloned into the mammalian pBJ1-neo expression vector, and the resulting construct is transfected into the class I-negative EBV-transformed lymphoblastoid line 721.221. The soluble class I HLA occupied with endogenous peptide is then collected from the bioreactor and adsorbed onto a BBM.1 (anti-β2m) antibody-Sepharose 4B column. Further downstream processing of the complexes (*i.e.,* extraction of the peptides from the HLA complexes) deviates from that taught by McClusky *et al*, as Prilliman *et al* did not wish to maintain the integrity of the complexes.

Thus, Prilliman et al teach that soluble human class I MHC complexes consisting of MHC class I heavy chain, β2m light chain and occupied with endogenous peptides can be produced by creating constructs that lack the coding regions for the transmembrane and cytoplasmic domain, can be produced as soluble molecules in high yield in a hollow fiber bioreactor unit, and can be adsorbed onto a mAb-affinity column and eluted from said column. Prilliman, do not, however, teach isolating mRNA, nor do they teach isolating the affinity-purified class I MHC complexes without further downstream processing.

DiBrino *et al* do provide the teaching of isolating mRNA encoding a truncated class I MHC heavy chain. DiBrino *et al* teach making a truncated HLA class I heavy chain lacking the transmembrane and cytoplasmic regions by PCR amplification of an HLA-B44 cDNA clone using specific primers and a prokaryotic *E. coli* plasmid expression vector (amino acid residues 1-278), that can be combined *in vitro* with β2m light chain and peptide to form MHC class I complexes. DiBrino *et al* also teach obtaining and full length cDNA for HLA-B*4403 by PCR amplification of cDNA made from RNA isolated from the immortalized human lymphoblastoid B cell line W1B. The cDNA was sequenced to confirm identity of the heavy chain, cloned into the mammalian expression vector RSV.neo and transfected into Hmy2.C1R cells, where they are expressed on the cell surface in complex with β2m and endogenous peptides (class I deficient cell line). DiBrino *et al* teach detection of said HLA using W6/32 monoclonal antibody specific for human Class I molecules (especially materials and methods section).

Thus, DiBrino et al teach that the heavy chain of a MHC class I molecule can be constructed so that it lacks the TM and cytoplasmic regions, and that the heavy chain is capable of associating in vitro with β2m light chain and peptide to form MHC class I complexes. DiBrino et al also teach that the full-length heavy chain encoded construct, when transfected into a mammalian host cell, can associate with β2m light chain, acquire endogenous peptide and be transported to the cell surface.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced a soluble MHC class I complex similar to the complex disclosed by U.S. Patent No. 5,482,841, except instead of a full-length molecule, making one that comprises a truncated version of an MHC class I, said truncated version being a soluble intact class I MHC molecule complex consisting of the MHC class I heavy chain extracellular regions and lacking the TM and cytoplasmic domains, and β2m and endogenous peptide from the host cell, using the 3' primer type taught by Prilliman *et al* or *DiBrino et al*, and the inserting, electroporating, inoculating, culturing and immunoaffinity purification steps taught by Prilliman *et al (i.e.,* creating a mammalian plasmid encoding vector for a truncated heavy chain lacking the transmembrane and cytoplasmic regions, transfecting the expression vector into a suitable host cell, inoculating a hollow fiber bioreactor, harvesting the soluble class I MHC complexes from the said hollow fiber bioreactor unit, and isolating them by immunoaffinity purification as intact complexes), but starting with mRNA as taught by DiBrino *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce large quantities of soluble, truncated and intact MHC class I complexes as taught by Prilliman *et al* to be used in the method for anti-MHC class I antibody detection as disclosed by U.S. Patent No. 5,482,841, particularly in light of the teaching of McClusky *et al* that a secreted version of MHC class I complexes is particularly valuable because it is a monovalent, soluble, homogenous, recombinant protein that is free of detergent, lipid or cellular membrane components.

Hausmann *et al* teach isolated HLA-A2 complexes that have been papain solublized (*i.e.,* they are soluble and lack the transmembrane and cytoplasmic domains) from the MHC-class I bearing EBV-transformed spleen cell line M4 (*i.e.,* a mammalian cell line) and isolated by affinity chromatography with anti-HLA-A2 antibodies (with elution at pH 11.5 prior to neutralization), wherein the complexes comprise the MHC class I heavy chain extracellular regions without the transmembrane and cytoplasmic domains, non-covalently associated β2m and an endogenously loaded MHC class I binding peptide bound in the peptide binding groove. Hausmann *et al* teach that these class I MHC complexes are useful for the study of T cell reactivity against foreign MHC products in transplantation settings, as well as for study of immunomodulation (especially abstract, introduction, materials and methods, page 184, column 1, first two paragraphs, paragraph spanning pages 185-186).

Chen *et al* teach that elution at pH 11.5 of MHC class I molecules from anti-class I antibody affinity columns does not dissociate the complex, nor elute endogenous peptides from the antigen binding groove of MHC class I molecules (especially page 2875 at the paragraph spanning columns 1-2 and the paragraph spanning pages 2876-2877).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have collected the immunoaffinity purified intact complexes taught by Prilliman *et al* ***without*** subjecting them to the further downstream processing that is taught by Prilliman *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce intact complexes as taught by Hausmann *et al,* especially since Hausemann *et al* teach that these intact complexes are useful for study of alloreactivity.

In addition, the instant claims are included in this rejection because although Prilliman *et al* do not explicitly teach wherein the soluble class I HLA complexes after harvesting and acid elution from the anti-β2m-Sepharose 4B immunoaffinity complexes are intact complexes with the conformation of the native complexes prior to said step, said art reference does teach that further acidification is required to denature the class I heavy chain-β2m-peptide complexes in order to liberate the bound peptides. Therefore, the claimed process appears to be similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Alternatively, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have eluted the HLA class I complexes from the immunoaffinity column by any art known method that would preserve the conformation and integrity of the complexes, such as by the methodology taught by Hausmann *et al* and Chen *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to generate soluble forms of HLA class I molecules to for the assay disclosed by the primary reference.

It would have also been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the human class I MHC-specific W6/32 mAb taught by DiBrino *et al* in the immunoaffinity purification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because DiBrino *et al* teach that this mAb is specific for human class I MHC, Prilliman *et al* teach using a class I MHC negative mammalian host cell in order to produce the soluble, truncated MHC class I molecules, and DiBrino *et al* teach using a class I MHC deficient cell line for this same purpose, *i.e.,* W6/32 can bind to all human class I MHC molecules, but only one specific soluble MHC class I allele product is being produced and isolated.

Claim 46 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have optimized the method of expression by insuring that the mammalian expression vector contains a promoter that facilitates increased expression of the PCR product, as was routine in the art.

Applicant's arguments (of record in the amendment and response filed 5/24/10 on pages 8-10) are moot in light of this ground of rejection.

11. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of McClusky *et al* (J. Immunol. 1988 141: 1451-1455), Prilliman *et al* (Immunogenetics, 1997, 45: 379-385, IDS reference), DiBrino *et al* (Biochemistry 1995, 34(32):10130-10138, of record), Hausmann *et al* (Clin. Exp. Immunol. 1993, 91: 183-188) and Chen *et al* (J. Immunol. 1994, 152: 2874-2881) as applied to claims 31-37, 42, 45, 46, 49-51, 60 and 61 above, and further in view of Nakajima and Yaoita (Nucleic Acids Res. 1997, 25(11): 2231-2232).

U.S. Patent No. 5,482,841, Hausmann *et al*, Prilliman *et al* and DiBrino *et al* have been discussed supra.

The combination of U.S. Patent No. 5,482,841, Hausmann *et al*, Prilliman *et al* and DiBrino *et al* does not teach wherein the locus-specific primer includes a sequence encoding a tail that is used to facilitate purification of the soluble class I MHC complexes.

Nakajima and Yaoita teach that the advantage of epitope tagging a recombinant protein using PCR is that by adjoining an epitope peptide to a protein of interest, a commericially available antibody to the epitope substitutes for an antibody to a recombinant protein (see entire reference, especially abstract and first paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a epitope tag (or 'tail") to the encoded MHC class I heavy chain after the $\alpha 3$ extracellular region.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to facilitate purification of MHC complexes using a purification tail at the 3' end, without interfering with peptide binding at the 5' end of the heavy chain that forms the peptide binding groove.

Applicant's arguments (of record in the amendment and response filed 5/24/10 on pages 8-10) are moot in light of this ground of rejection.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644